The NIH-sponsored Diabetes Prevention Program clinical trial demonstrated that through modest weight loss and exercise, people at risk of developing type 2 diabetes can delay or prevent its onset. The "Small Steps. Big Rewards. Prevent Type 2 Diabetes" campaign spreads this important prevention message of hope. The campaign is led by the National Diabetes Education Program (NDEP), which is a partnership of the NIDDK of the NIH, the CDC, and over 200 public and private organizations. The NDEP has created tailored materials and messages for audiences at high risk of developing type 2 diabetes, including African Americans, Hispanic and Latino Americans, American Indians and Alaska Natives, Asian Americans and Pacific Islanders, and older adults. Campaign information and materials can be found at *http://ndep.nih.gov/campaigns/SmallSteps/SmallSteps_index.htm*.

Diabetes, Endocrinology, and Metabolic Diseases

NIDDK support of basic and clinical research in the areas of diabetes, endocrinology, and metabolic diseases spans a vast and diverse range of diseases and conditions, including diabetes, osteoporosis, cystic fibrosis, and obesity. Together, they affect many millions of Americans and profoundly decrease their quality-of-life. Many of these diseases are complex—an interplay between genetic and environmental factors contributes to disease development.

Diabetes is a debilitating disease that affects an estimated 18.2 million people in the U.S.—over 6 percent of the total population—and is the sixth leading cause of death. Diabetes lowers average life expectancy by up to 15 years, increases cardiovascular disease risk two-to-four-fold, and is the leading cause of kidney failure, lower limb amputations, and adult-onset blindness. In addition to these human costs, the estimated total financial cost for diabetes in the U.S. in 2002—including costs of medical care, disability, and premature death—was $132 billion. Effective therapy can prevent or delay these complications, but approximately one third of Americans with diabetes are undiagnosed.

Diabetes is characterized by the body's inability to produce and/or respond appropriately to insulin, a hormone which is necessary for the body to absorb and use glucose (sugar) as a cellular fuel. These defects result in persistent elevation of blood glucose levels and other metabolic abnormalities, which in turn lead to the development of disease complications. The most common forms of diabetes are type 1 diabetes, in which the body completely loses its ability to produce insulin; and type 2 diabetes, in which the body becomes resistant to insulin signaling, and which can eventually result in impaired insulin production.

Type 1 diabetes affects approximately 5 to 10 percent of individuals with diagnosed diabetes. It most often occurs in children, but may appear at any age. Type 1 diabetes is an autoimmune disease, in which the immune system mistakenly attacks and destroys the beta cells of the pancreas. These beta cells, which are found within tiny cell clusters called islets, are the body's sole producers of insulin. If left untreated, type 1 diabetes results in death from starvation despite high levels of glucose in the bloodstream. Thus, patients require lifelong insulin administration—in the form of multiple daily injections or via an insulin pump—in order to regulate their blood glucose levels. Despite vigilance in disease management, with frequent finger sticks to test blood glucose levels and the administration of insulin, it is still impossible for patients to control blood glucose levels as well as they could if they had functional beta cells. Thus, researchers are actively seeking new methods to improve blood glucose monitoring and insulin delivery, as well as working on new beta cell replacement therapies meant to cure type 1 diabetes.

Type 2 diabetes is the most common form of the disease, accounting for up to 95 percent of diabetes cases in the U.S. Type 2 diabetes is associated with several factors, including older age and a family history of diabetes. It is also strongly associated with obesity: more than 80 percent of people with type 2 diabetes are overweight or obese. Type 2 diabetes occurs more frequently among minority groups, including African Americans, Hispanic Americans, American Indians, and Native Hawaiians.

In patients with type 2 diabetes, cells in muscle, fat, and liver tissue do not properly respond to insulin. Gradually, the pancreatic beta cells secrete less and less insulin, and the timing of insulin secretion becomes abnormal. To control glucose levels, treatment approaches include diet, exercise, and medications; some patients also need to take insulin. There are also millions of individuals who have a condition called "pre-diabetes," in which blood sugar levels are higher than normal, but not as high as in diabetes. This population is at high risk of developing diabetes. Fortunately, the Diabetes Prevention Program (DPP) clinical trial has shown that patients with pre-diabetes can dramatically reduce their risk of developing full-blown diabetes with improvements in lifestyle or with drug treatment.

Type 2 diabetes was previously called "adult-onset" diabetes because it was predominantly diagnosed in older individuals. However, this form of diabetes is increasingly being diagnosed in children and adolescents, and it disproportionately affects minority youth. Believed to be related to increasing rates of pediatric obesity, this is an alarming trend for many reasons. First, the onset and severity of disease complications correlate with the duration of diabetes; thus, those with early disease onset are at greater risk with respect to complications. Second, maternal diabetes during pregnancy—either onset of type 2 diabetes before pregnancy or the development of gestational diabetes during pregnancy—confers an increased risk of diabetes in offspring. Thus, the rising rates of diabetes and pre-diabetes in young women could lead to a vicious cycle of ever-growing rates of diabetes. Third, diabetes often becomes more difficult to control over time. With longer duration of disease, health care providers may find it increasingly difficult to strictly control a patient's blood sugar and thus prevent or delay the development of complications. Therefore, the advent of type 2 diabetes in youth has the potential to drastically worsen the enormous health burden that diabetes already places on the U.S.

The NIDDK is supporting research to better understand the mechanisms that lead to the development and progression of diabetes and the many other endocrine and metabolic diseases within the Institute's mission; such research will ultimately spur the design of potential new intervention strategies. In parallel, based on knowledge from past scientific research investments, the Institute is vigorously pursuing studies of prevention and treatment approaches for these diseases.

ADVANCES AND OPPORTUNITIES IN DIABETES RESEARCH

New Imaging Technology To Monitor Type 1 Diabetes Disease Progression: Type 1 diabetes is usually diagnosed very late in disease progression, when most of the beta cells of the pancreas (which produce insulin) have already been destroyed by an autoimmune attack. Currently, there is no way to detect the first signs of beta cell destruction to monitor disease progression. In research toward overcoming this major research and clinical barrier, scientists discovered a new, non-invasive imaging technology that enabled them to monitor disease progression in a mouse model. The technology uses a vascular probe, containing magnetic nanoparticles that can be detected by magnetic resonance imaging (MRI). If type 1 diabetes has already begun to develop, the probe leaks out of the blood vessels of the pancreas and can be visualized by MRI. Vascular probes have already been successfully used in humans to detect prostate cancer metastases; therefore, this technology has high potential of being translated to the clinic for type 1 diabetes. Importantly, this technology can facilitate studies of the molecular underpinnings of disease onset and progression, which can lead to novel prevention and treatment strategies.

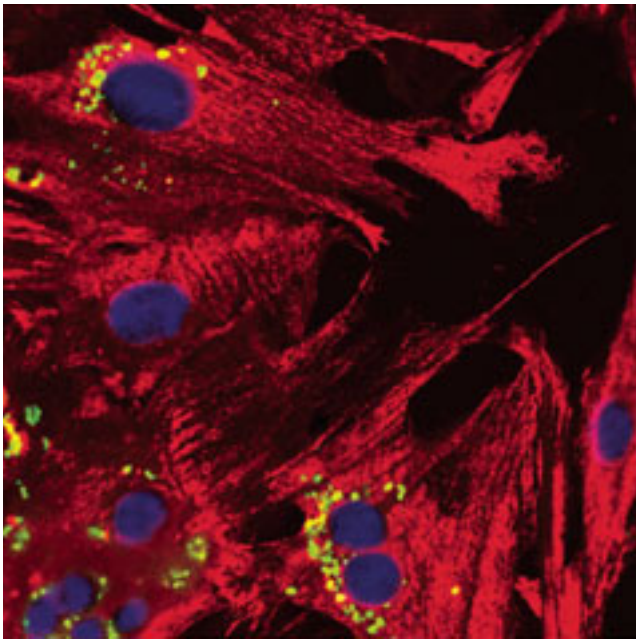
Denis MC, Mahmood U, Benoist C, Mathis D, and Weissleder R. Imaging inflammation of the pancreatic islets in type 1 diabetes. *Proc Natl Acad Sci USA* 101: 12634-12639, 2004.

Potential Source of Islet Cells for Future Cell Therapies: Research is helping to build understanding of beta cell regeneration, with implications for potential diabetes treatments. Scientists at the NIDDK's intramural laboratories have induced human insulin-producing cells to revert to islet precursor cells, proliferate, and then differentiate into islet-like cells again. The researchers first removed islets from human cadaver pancreata, and exposed these islets to a medium containing animal serum. Over time, cells migrated out until the original islets were depleted. These migrating islet cells, identified as insulin-expressing cells, then turned into more primitive precursor cells that do not produce insulin. These new cells, called human islet-derived precursor cells, reproduce easily to form many more cells. They also appear to naturally and efficiently differentiate into clusters of islet-like cells when subsequently exposed to a serum-free medium. The differentiated cells produce much less insulin than the original cells, but do show many of the characteristics of the original beta cells. While these cells appear to be different from stem cells, the scientists noted that their studies do not preclude the possibility that adult islet stem cells may exist. For the future, the researchers hope to define the optimal environmental conditions to grow precursor cells and to stimulate them to differentiate into hormone-producing cells. Their goal is to design a cellular environment as close as possible to the natural environment of a healthy human pancreas. Another challenge is to develop a culture medium that does not rely on animal serum, so cells grown in the laboratory could be transplanted back into people with a minimum risk of side effects. Because of the relatively small number of cadaveric donor pancreata available for transplantation, research toward developing new sources of islet cells is critical for future therapeutic use.

Gershengorn MC, Hardikar AA, Wei C, Geras-Raaka E, Marcus-Samuels B, and Raaka BM. Epithelial-to-Mesenchymal Transition Generates Proliferative Human Islet Precursor Cells. *Science* 306: 2261-2264, 2004.

Defects in the Cell's Energy-converting Machines, Mitochondria, Are Linked to Type 2 Diabetes and Cardiovascular Disease Risk Factors: Mitochondria are components of cells that can extract energy from molecules derived from food and convert it into a form that is used to fuel the cell's biological processes; in certain cells, the mitochondria dissipate energy from food sources as heat, rather than storing it in a form for future use. While some components of mitochondria are encoded by genes in the cells' nucleus, where most of the cell's genetic material resides, mitochondria also harbor their own separate genomes. Researchers exploring the underpinnings of diabetes and other metabolic problems have recently identified mitochondrial defects as potential contributing factors to these health conditions.

To improve medical strategies for the prevention of diabetes, it is important to know the precise mechanisms underlying disease development. While obesity is a serious risk factor for type 2 diabetes, it does not fully explain the disease, because many obese people are not diabetic, and some people of normal weight develop diabetes. Identification of the biologic basis for diabetes susceptibility is key to development of new therapies. Several recent lines of evidence suggest that people with type 2 diabetes may have defects in the functioning of mitochondria, the structures in cells responsible for converting fat into useful energy. A new study reports that these defects precede the development of the disease: people at risk for type 2 diabetes accumulate fats in muscle cells, and this accumulation correlates with mitochondrial problems. Because the presence of such fats has been shown in experimental models to decrease the ability of cells to function properly in response to insulin, deficits in mitochondrial function could potentially contribute to the insulin-resistance that can lead to type 2 diabetes. These insights may help pave the way to the development of therapies aimed at correcting mitochondrial function as a possible means of preventing or delaying onset of the disease.



In laboratory studies, scientists at the NIDDK have induced insulin-producing cells, obtained from human pancreatic tissue, to revert to islet precursor cells. These precursor cells are capable of expansion and appear to naturally and efficiently differentiate into clusters of islet-like cells. The image shows cells during a laboratory experiment in which insulin-expressing human cells were induced to form islet precursor cells. This work may help to clarify the natural lifecycle of the beta cell and may eventually have applications for diabetes treatment. Photo courtesy of Dr. Marvin C. Gershengorn, NIDDK, and reprinted from Gershengorn et al. *Science*, online publication 25 November 2004, 10.1126/science.1101968; print: *Science* 306: 2261-4.

Another group of scientists sought to discover genetic factors that may contribute to a clustering of certain metabolic defects by studying a large family in which many members suffered from these conditions. The metabolic defects included hypertension and abnormal blood lipids (fat molecules)—conditions that often occur together for reasons that have not been clear—as well as defects in levels of blood magnesium. The scientists traced these medical conditions in the large family to a mutation in the mitochondrial genome. The results of this study may direct future investigations of potential mitochondrial defects as contributing to the clustering of hypertension, blood lipid abnormalities, and other metabolic problems commonly seen in the population.

Petersen KF, Dufour S, Befroy D, Garcia R, and Shulman GI. Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. *N Engl J Med* 350: 664-671, 2004.

Wilson FH, Hariri A, Farhi A, Zhao H, Petersen KF, Toka HR, Nelson-Williams C, Raja KM, Kashgarian M, Shulman GI, Scheinman SJ, and Lifton RP. A Cluster of Metabolic Defects Caused by Mutation in a Mitochondrial tRNA. *Science* 306: 1190-1194, 2004.

Patient Literacy Affects Success of Type 2 Diabetes Disease Management: Patients with diabetes can minimize complications by reducing the level of sugar in their blood. While many diabetes disease management programs have helped patients reduce their blood sugar levels by using a combination of education, medication, diet and exercise regimens, and glucose monitoring, their use in socially disadvantaged populations has been less successful. Low literacy is common among patients and is associated with poor knowledge about diabetes. A recent study examined the role of literacy on the effectiveness of a comprehensive disease management program for patients with type 2 diabetes. In the study, half of the 217 patients received usual care from their primary care clinician, while the rest received usual care plus supplemental intensive diabetes management that included one-on-one counseling and medication management. The individualized care included tools to enhance comprehension such as simplified verbal explanations, picture-based materials and "teach-back" patient comprehension assessments. The supplemental intervention significantly improved the blood sugar control in patients with low literacy (below sixth-grade level). Patients with higher literacy showed improvement from the usual care regardless of whether or not they also received the individualized care. These results suggest that providing individualized care can improve the success of diabetes management, and that patients with low literacy stand to benefit the most from such care.

Rothman RL, DeWalt DA, Malone R, Bryant B, Shintani A, Crigler B, Weinberger M, and Pignone M. Influence of patient literacy on the effectiveness of a primary care-based diabetes disease management program. *JAMA* 292: 1711-1716, 2004.

Examples of New NIDDK Clinical Research Efforts on Type 1 Diabetes: The NIDDK is pursuing a variety of avenues of clinical research on type 1 diabetes. Several new studies are being conducted by Type 1 Diabetes TrialNet. TrialNet is an international network of investigators, clinical centers, and core support facilities whose aim is to recruit patients and support studies that will result in an improved understanding of type 1 diabetes disease development and will test strategies for its prevention. TrialNet is spearheaded by the NIDDK and is co-sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Child Health and Human Development (NICHD), and the Juvenile Diabetes Research Foundation International (JDRF). The TrialNet's Type 1 Diabetes Natural History Study will probe the causes of type 1 diabetes by examining the immune and metabolic events leading to disease onset in individuals who are at-risk for disease development. TrialNet also recently launched a study to test two immunosuppressive agents—mycophenolate mofetil and daclizumab—to determine if they are able to safely delay or stop the immune destruction of remaining beta cells in new-onset type 1 diabetes patients. Another new TrialNet effort is a pilot clinical study based on observations from epidemiologic studies that children who have received omega-3 fatty acid—either in the womb or during the first year of life—have a lower risk of developing type 1 diabetes. Epidemiologic studies are useful for generating hypotheses to be tested in randomized clinical trials. The new pilot clinical study will assess the feasibility of a large scale trial to determine whether nutritional supplements with an omega-3 fatty acid will prevent the development of islet autoimmunity.

The NIDDK, in another international effort, also in partnership with NIAID, NICHD and JDRF as well as the National Institute of Environmental Health Sciences and the CDC, has begun recruitment for a study that will seek to identify infectious agents, dietary factors, and/or other potential environmental conditions that might trigger type 1 diabetes in genetically susceptible newborns. This study is called The Environmental Determinants of Diabetes in the Young (TEDDY).

The NIDDK, in collaboration with the National Institute of Allergy and Infectious Diseases, has also recently funded a new Clinical Islet Transplant (CIT) consortium. The consortium's studies will focus on improving the safety and long-term success of methods for transplanting islets in people with type 1 diabetes.

The Type 1 Diabetes - Rapid Access to Intervention Development (T1D-RAID) is a cooperative program of the NIDDK and the National Cancer Institute designed to facilitate translation to the clinic of novel, scientifically meritorious therapeutic interventions. It will do this by making available, on a competitive basis, NCI resources for the pre-clinical development of drugs, natural products, and biologics. A partial listing of those services includes: high-throughput screening, studies in animal models, formulation, pharmacology and toxicology studies, and bulk substances acquisition. T1D-RAID is intended to remove the most common barriers between laboratory discoveries and clinical trials of new molecular entities. The goal of T1D-RAID is to support the preclinical work needed for the clinical "proof of principle," which is the study that will determine if a new molecule or novel approach is a viable candidate for expanded clinical evaluation.

Finally, the NIDDK has expanded its Web pages on the Special Statutory Funding Program for Type 1 Diabetes Research, which it administers on behalf of the Secretary, HHS, and in which multiple NIH components and the CDC participate. These Web pages include resources for investigators, such as funding opportunities and availability of tools and materials for research, as well as information for patients and family members on clinical studies in which they may wish to participate.

Building on the Success of the Diabetes Prevention Program (DPP) Clinical Trial: The NIDDK is pursuing several efforts to build upon the findings of the landmark NIH-sponsored Diabetes Prevention Program (DPP) clinical trial. The DPP examined the effects of lifestyle and medical interventions on the development of type 2 diabetes in adults at risk

for this disease. Upon entering the trial, the over 3,000 participants had elevated blood glucose levels and were overweight, and thus were at substantial risk for developing type 2 diabetes. Nearly one-half of the participants were from minority groups, and approximately two-thirds were women. The lifestyle intervention included modest weight loss and exercise. The results of the lifestyle intervention demonstrated a dramatically reduced risk—by 58 percent—of developing type 2 diabetes in a population at high risk. The medication intervention using the drug metformin reduced diabetes risk by 31 percent. The lifestyle and metformin interventions worked well in both men and women and in all ethnic groups studied; the lifestyle intervention was also particularly effective in older participants.

"Small Steps. Big Rewards. Prevent Type 2 Diabetes"—Importantly, the dramatic health benefit resulting from the lifestyle intervention of DPP required only modest weight loss and exercise. This concept is now part of a new educational campaign to promote the findings of the DPP, called "Small Steps. Big Rewards. Prevent Type 2 Diabetes." The campaign is led by the National Diabetes Education Program (NDEP), which is a partnership of the NIDDK of the NIH, the CDC, and over 200 public and private organizations. The NDEP has created tailored campaign messages and materials for high risk audiences: African Americans, Hispanic and Latino Americans, American Indians and Alaska Natives, Asian Americans and Pacific Islanders, and older adults, as well as materials for a general audience. In addition, the NDEP and its partners are promoting diabetes prevention to health care providers to give them the information and tools to help their patients take small but important steps to prevent the disease. Additional information on the "Small Steps. Big Rewards. Prevent Type 2 Diabetes" campaign is presented in the sidebar on the NDEP, in this chapter. Information and campaign materials are also available at: *http://ndep.nih.gov/campaigns/SmallSteps/SmallSteps_index.htm.*

Assessing the Durability of the DPP Interventions: The DPP Outcomes Study (DPPOS)—The DPPOS is a follow-up study of participants in the DPP clinical trial. The DPPOS will examine the durability of the DPP interventions on prevention or delay of type 2 diabetes and its cardiovascular complications; heart disease is the major cause of death in people with type 2 diabetes. The DPPOS will additionally examine the ability to maintain weight loss in the participants over extended periods of time. The study will also investigate other associated health conditions in the participants, including, for example, kidney disease and urinary incontinence.

Research Demonstration and Dissemination Projects: Bringing the DPP Results to Patients—The NIDDK is supporting studies to test and evaluate interventions and activities that lead to the application of existing knowledge to disease control and prevention. Among these studies are research projects aimed toward improving translation—in this case, from clinical trial to community patient care—of the results of the DPP. For example, in one study, working with families in whom at least one member has type 2 diabetes, researchers are testing a "family visit program" to help all family members learn how they can adopt healthy lifestyles and better use healthcare and other community resources. The study is being conducted in an area with a substantial Hispanic population. Examples of other translational research projects include studies of a primary care and Web-based intervention for adolescents at risk for diabetes, an intervention that targets couples in which one spouse has type 2 diabetes, and a community-based, family-oriented health program to decrease obesity and risk of type 2 diabetes in children from a high risk, inner-city African American population.

THYROID HORMONE DISORDERS

Thyroid Hormone Requirements During Pregnancy: Thyroid hormone (TH) plays an important role in promoting normal fetal development during pregnancy. When maternal TH levels are too low (hypothyroidism) or too high (hyperthyroidism), the result could be increased fetal mortality or other fetal developmental problems. Hypothyroidism is treated with a synthetic form of TH, called

levothyroxine. Pregnancy increases the requirement for TH, so the dose of levothyroxine in women with hypothyroidism is increased during pregnancy, usually after the first prenatal doctor's visit at approximately 10 weeks of gestation. However, it is unclear if this timing is sufficient to protect the fetus from harmful effects of low TH levels. To learn the timing pattern of TH requirement during pregnancy, researchers studied 19 women who had hypothyroidism and desired pregnancy. They determined that the requirement for increased levothyroxine occurs very early in pregnancy—as early as the fifth week of gestation. Based on these novel observations, the researchers recommend that women with hypothyroidism be counseled before pregnancy to increase their levothyroxine dose immediately upon confirming pregnancy, even before their first prenatal doctor's visit. Another study investigated the opposite situation—the effects of high TH levels on the developing fetus. Researchers studied individuals who have "resistance" to thyroid hormone (RTH), and whose thyroid produces very high levels of TH in compensation. Because mothers with RTH make high levels of TH during pregnancy, the researchers could investigate the effects of high TH levels on the fetus. The researchers observed a 3- to 4-fold increase in the rate of miscarriage in the women with RTH. In addition, they observed differences in birth weights of the babies born to women with RTH. When the newborn also had RTH, the birth weight was normal; however, if the newborn did not have RTH, the birth weight was low. These results suggest that high levels of TH could be damaging to the fetus and result in increased rates of miscarriage and low birth weights. Thyroid disorders are prevalent in women and TH is one of the most commonly prescribed medications. Taken together, these studies emphasize the importance of maintaining normal TH levels during pregnancy and suggest adjustment of TH medicines earlier in pregnancy than is the current practice.

Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, and Larsen PR. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. *N Engl J Med* 351: 241-249, 2004.

Anselmo J, Cao D, Karrison T, Weiss RE, and Refetoff S. Fetal loss associated with excess thyroid hormone exposure. *JAMA* 292: 691-695, 2004.

CYSTIC FIBROSIS

Curcumin as a Potential Treatment for Cystic Fibrosis: Cystic fibrosis (CF) is a genetic disorder that results in the accumulation of thick, sticky mucus in the lungs, causing damage and facilitating infections. CF is caused by mutations in the gene encoding the CFTR protein, which resides in the outer surface of cells lining such tissues as the lung and intestine, where it regulates the movement of chloride. The most common mutation of the gene, ΔF508, yields a protein that would be functional, but which is degraded before it reaches the cell surface. Researchers have recently tested the effect of a compound called curcumin, purified from the spice turmeric, in a mouse model of CF. When given to mice that are genetically engineered to have the ΔF508 mutation, curcumin treatment enabled the mutant form of the CFTR protein to function effectively, presumably by allowing it to reach its normal cellular destination. Indeed, when cells cultured from animals with the ΔF508 mutation were treated with curcumin, the protein was properly routed to the cell surface. Importantly, the amount of curcumin that achieved these promising results in mice is equivalent to a dose that has been well-tolerated by humans in previous studies. Therefore, curcumin, which is already known to be safe in people, has the potential to be of value for patients with this devastating illness.

Egan ME, Pearson M, Weiner SA, Rajendran V, Rubin D, Glöckner-Pagel J, Canny S, Du K, Lukacs GL, and Caplan MJ. Curcumin, a major constituent of turmeric, corrects cystic fibrosis defects. *Science* 304: 600-602, 2004.

NIDDK AIDS RESEARCH

Research supported by the NIDDK has contributed to the current understanding of AIDS wasting syndrome. With the widespread adoption of highly active antiretroviral therapy (HAART), which has markedly

improved survival, the incidence of AIDS wasting syndrome has declined. Unfortunately, HAART and HIV infection are associated with a variety of metabolic complications, collectively termed "lipodystrophy syndrome." This syndrome may include abnormal distribution of body fat, dyslipidemia (elevated levels of unhealthy fats in the blood) and insulin resistance. These metabolic abnormalities are major risk factors for the development of serious diseases, such as diabetes and cardiovascular disease. The NIDDK supports a number of research studies aimed at understanding the causes and exploring possible therapies for HIV-associated lipodystrophy.

Hormonal Treatment for HIV-infected Men with Lipodystrophy: Some HIV-positive men with lipodystrophy and excess abdominal fat have reduced levels of growth hormone (GH). Restoring GH to normal levels is a potentially attractive approach to treating these individuals, as GH has been shown to reduce visceral fat in GH-deficient patients. Unfortunately, high-dose GH therapy can result in insulin resistance and other complications. An alternative strategy to normalize GH levels is to provide an agent that promotes increased secretion of GH by the pituitary gland, such as growth hormone-releasing hormone (GHRH). Researchers recently compared GHRH therapy with placebo (sugar pill) in 31 HIV positive men with lipodystrophy over 12 weeks. The effectiveness of the treatment was determined by measuring levels of IGF-1, a protein secreted in response to GH stimulation that mediates many of its actions. GHRH therapy significantly increased levels of IGF-1 in treated individuals, and was associated with significant improvements in a number of body mass parameters, including increased lean body mass, decreased trunk fat, and reduced abdominal visceral fat. Levels of blood glucose, insulin, and lipids did not change significantly. GHRH therapy, which is aimed at returning GH to a more normal range, may be beneficial in HIV positive individuals with diminished levels of the hormone. GH concentration might not reach harmful levels during treatment with GHRH because other factors that are also influenced by this hormone are present to provide feedback into GH production, if it becomes too high. GHRH therapy may therefore represent a more "natural" way of restoring GH levels to the normal range.

Koutkia P, Canavan B, Breu J, Torriani M, Kissko J, and Grinspoon S. Growth hormone-releasing hormone in HIV-infected men with lipodystrophy: a randomized controlled trial. *JAMA* 292: 210-218, 2004.

Liver disease is an important cause of sickness and death in persons infected with HIV. HIV-infected persons, like non-HIV infected persons, can develop hepatitis B and C, NASH, alcoholic liver disease, drug-induced liver disease, and opportunistic infections of the liver and biliary tree. In HIV-infected persons receiving HAART, liver disease caused by chronic viral hepatitis has emerged as a leading cause of death, due in large part to hepatitis C virus (HCV) co-infection, a consequence of a shared transmission route for the two viruses. HCV infection is adversely affected by co-infection with HIV at every stage of its natural history; the proportion of patients who recover is much lower, and the disease progresses from persistent infection to cirrhosis to end-stage liver disease more rapidly. As therapies for HIV have improved and survival has been extended by antiretroviral therapy, liver disease has become a critical problem among HIV-infected persons. The major goals for NIDDK research in HIV and liver disease are to define the causes of liver disease associated with HIV, including interactions between HIV and hepatitis viruses, and to develop means to prevent and treat liver disease in HIV-infected people.

The NIDDK also supports a productive structural biology program within the Institute itself. These projects seek to determine the structures of biologically significant proteins relative to HIV infection, replication, and integration. Through a greater understanding of these structures, the underlying mechanisms of HIV infection are illuminated. Determination of the structure of these proteins is critical for understanding the mode of action of these important molecules and it is also an essential first step in the development of drugs to treat and prevent HIV infection.

Collaborative Islet Transplant Registry – First Report Published

Researchers from 12 medical centers in the United States and Canada, who have performed islet transplants in 86 patients with type 1 diabetes, published their results in the first annual report of the Collaborative Islet Transplant Registry (CITR). The CITR's mission is to expedite progress and promote safety in islet transplantation by collecting, analyzing, and communicating data on this experimental therapeutic procedure. The CITR is supported by a Special Statutory Funding Program for Type 1 Diabetes Research. The report (*www.citregistry.org*) analyzes many factors that can affect the outcome of this experimental procedure for people with severe or complicated type 1 diabetes. It provides data on recipient and donor characteristics, pancreas procurement and islet processing, immunosuppressive medications, function of the donated islets, patients' lab results, and adverse events.

Type 1 diabetes, which affects up to 1 million people in the United States, develops when the body's immune system destroys the insulin-producing beta cells of the pancreas. This form of diabetes usually strikes children and young adults, who need several insulin injections a day or an insulin pump to survive. Insulin, however, is not a cure, and eventually most people with type 1 diabetes develop one or more complications of the disease, including damage to the heart and blood vessels, eyes, nerves, and kidneys. From 1990 to 1999, only 8 percent of islet transplants resulted in insulin independence for more than 1 year. In 2000, however, a group of researchers at the University of Alberta in Edmonton, Canada, reported much greater success in patients transplanted with islets from two to four donor pancreata and treated with an immunosuppressive regimen that left out glucocorticoids, now thought to be toxic to islets. In the next few years, other researchers replicated the "Edmonton protocol" pioneered by the Canadian team, and many centers are now using this approach to islet transplantation.

In islet transplantation, as performed by the 12 participating centers presented in the CITR report, insulin-producing cells derived from donor pancreata were infused into patients with difficult-to-control type 1 diabetes though the portal vein of the liver. When successful, the transplanted islets took up residence in the liver's small blood vessels and began producing insulin. The 86 recipients, who had type 1 diabetes for an average of 30 years, received a total of 158 infusions of islets extracted from 173 donor pancreata. Twenty-eight patients received one islet infusion, 44 received two, and 14 received three. At 6 months after the last infusion, 61 percent of recipients no longer had to inject insulin. At 1 year after the last transfusion, 58 percent were still insulin independent. Some insulin-independent patients, although not receiving insulin, did have higher-than-normal blood glucose levels. Researchers will continue to monitor patients to see how long they remain insulin independent.

Recipients, 66 percent of whom were women, were an average age of 42 years (range 24 to 64 years) and average weight of 143 lbs. (range 103 to 213 lbs.). Before the procedure, nearly half the recipients were using an insulin pump. Most had recently experienced at least one episode of hypoglycemia, or dangerously low blood glucose, requiring another person's help. Their average level of hemoglobin A1c (HbA1c), which reflects blood glucose control over the previous three months, was 7.7 percent, compared to a normal HbA1c of 6 percent.

HbA1c levels generally improved with each infusion, as did levels of fasting blood glucose and C-peptide, which reflect insulin production. One infusion, though rarely providing enough islets to free a person from the need to inject insulin, alleviated episodes of severely low blood glucose. After the first infusion of islets, only two recipients had a low blood sugar problem requiring the

help of another person. None of those who received a single infusion reported a problem with hypoglycemia a year after the procedure.

The centers reported 45 serious adverse events but no deaths in the recipients. The 27 percent of events that were classified as life-threatening included those linked to the transplant procedure itself (e.g., infection, bleeding into the chest or abdomen, low hemoglobin, high liver enzymes) and events linked to medications that suppress the immune system (e.g., anemia, nerve damage, meningitis, and low numbers of white blood cells). Most recipients received the same drug regimen used in the Edmonton protocol: daclizumab at induction to prevent the immune system from rejecting the donor islets and sirolimus, combined with tacrolimus, to maintain immunosuppression.

The CITR is continuing to receive additional data from the inaugural 12 centers and from new centers joining and contributing data. Thus, future reports will be even more comprehensive. Recently, five islet transplant centers in Europe, with funding from the Juvenile Diabetes Research Foundation International (JDRF), began contributing data to the CITR. The CITR is also integrating data from other sources, such as the United Network for Organ Sharing (UNOS) and the Islet Cell Resource Centers. This collaborative effort will provide further critical information on factors that influence the success of islet transplantation.

Because only about 6,000 donor pancreata become available each year, and many are used for whole organ transplantation, the scarcity of islets poses a major obstacle to wider testing of islet transplantation as a treatment for type 1 diabetes. To improve the potential of cell replacement therapy for type 1 diabetes, NIH-funded research is focusing on understanding the beta cell and its regeneration and on efforts to develop alternative sources of beta cells. Researchers are also working on ways to coax the immune system into accepting donated cells or tissues without suppressing the whole immune system.

Hannah Beauregard

The Beauregard Family: What It Is Like to Care for a Young Child with Type 1 Diabetes

The day after two-and-a-half year old Hannah Beauregard had been diagnosed with type 1 diabetes, her parents, Doug and Mary, were being trained at their local hospital by a team of medical personnel on how to measure Hannah's blood glucose level. Blood glucose, or blood sugar, is measured in milligrams per deciliter of blood. Although people with diabetes have higher than normal blood sugar levels, they can also occasionally experience dangerous episodes of seriously low blood sugar. "At one point," Doug recalls, "I told the medical team that I must be doing something wrong because the monitor read 20 (milligrams per deciliter)." The proper target range for Hannah is substantially higher. Before he knew what was happening, attending residents whisked Hannah from his arms and out of her hospital bed into what Doug can only describe as a "little emergency-type" room. "They shut the door and would not allow me in," he vividly recalls.

Hannah Beauregard

What Doug didn't know at the time was that Hannah was being administered a medication that acts like "instant sugar." Because Hannah's blood sugar levels had dropped precipitously, this treatment was necessary to prevent her little body from going into a coma. What Doug did quickly realize was that having a child with diabetes was going to alter life for the Beauregard family dramatically.

"You Are Not Alone"

Doug Beauregard is a third grade teacher and longtime soccer coach. His wife, Mary, is a registered nurse. Given their professions, one would think that they should know a thing or two about children and medical care—and they do, a great deal. But having a young child with type 1 diabetes is often as difficult for them as it is for anyone else. "You're not alone," Doug wrote recently in an email to another parent seeking advice on how to deal with a toddler with type 1 diabetes who was refusing to eat after taking her insulin. "We're facing the same problem with Hannah."

Type 1 diabetes is an autoimmune disease that usually strikes early in life—most patients are diagnosed as children or young adults. Type 1 diabetes destroys the body cells that produce insulin (pancreatic beta cells). Without insulin, the body cannot properly metabolize glucose, a sugar that is the main source of fuel for cells. People with type 1 diabetes must carefully monitor their blood glucose levels throughout the day to determine when they need to eat, and administer insulin, either through injections or an

insulin "pump," to help their bodies use the glucose from carbohydrates in food. Both steps are also necessary to help keep blood sugar levels within a healthy target range. A constant challenge faced by people with type 1 diabetes is matching food intake, physical activity, and insulin doses in order to maintain healthy blood sugar levels; for example, although too little insulin leads to high blood sugar (hyperglycemia), administering too much insulin for the body's needs at a given time can cause blood sugar levels to fall too low (hypoglycemia). Dramatic rises and drops in blood sugar levels can have immediate and life-threatening consequences, and need to be avoided. Moreover, research has shown that carefully controlling blood sugar levels over the long-term is crucial to help prevent serious complications of diabetes, such as diabetic eye, kidney, and nerve disease, and cardiovascular disease.

According to Doug, since November 14, 2002, the day Hannah was diagnosed with type 1 diabetes, he has had only one night of uninterrupted sleep—and that night Doug was sick. "If Hannah snores, whimpers, cries, moves, or whatever, I wake up," he says. He can tell by the way she is sleeping if her blood sugar is low or high. "If I think it is low, I will check her. If not, I try to comfort her."

Doug and Mary love Hannah dearly. Doug, in particular, has made it his mission to tell everyone he can about Hannah and how special she is. "No one is responsible for Hannah's having type 1 diabetes. It's just part of her life, and we love her for who she is," says Doug, who actively tries to help other parents whose children have this life-threatening disease.

Communicating with Others

In many ways, Doug is the consummate communicator. The very first night that Hannah was diagnosed, Doug was on the Internet searching for local support groups. Today, he co-chairs a support group near the family's hometown of Plainwell, Michigan. The group consists of families of children with type 1 diabetes who range in age from 2 to 13 years old. Doug also frequently exchanges emails with people around the world, from Argentina to Newfoundland. "We are all seeking answers for our children," says Doug. "We learn a lot through each other's experiences and mistakes."

The Beauregards' support group meets for discussion and to listen to guest speakers, including representatives from companies who come to explain their product lines for people with diabetes. The group includes a 25-year-old who was diagnosed with type 1 diabetes when she was 15. "Heather describes for us what it was like to be a teenager with diabetes, as well as relates what it's like now to be an active, athletic young woman with the disease," says Mary. Heather is an accomplished volleyball player. Among other things, she serves as a role model for parents in the group who envision their young children as active young adults. Hannah, now 4 years old, takes dance lessons, and is a gymnast, as well as a downhill skier.

But What About All of Those Finger Pricks and Shots?

It is hard enough for adults with type 1 diabetes to take all of the steps necessary to take care of their disease. The question therefore remains, how does a parent convince a small child with type 1 diabetes that enduring finger pricks to test blood glucose levels and shots to administer insulin, several times a day, is necessary in order to stay alive and healthy? And how do parents feel about having to administer those finger pricks and shots?

To help the whole family adjust to Hannah's new health needs, the Beauregards introduced Hannah to a friend—a fluffy brown teddy bear named Rufus. Rufus™, The Bear with Diabetes, was given to Hannah by the organization Childrenwithdiabetes.com. Within hours of their meeting, Rufus became Hannah's fast friend. Rufus is designed so that he, too, needs to have his fingers "pricked" and to be given "shots." It wasn't long before Hannah was administering "shots" to Rufus. After finger pricks to test for glucose levels, both Hannah and Rufus would have their fingers

wiped and a special band-aid applied. When Hannah reminded her bear Rufus that it was time for his evening shot, she was really announcing to her parents that she was ready to have her own shot. The lesson: If Rufus can do it, Hannah can do it, too.

Everyone in Hannah's family—except 10-month-old Evan—knows how to care for her, including her 13-year-old brother, Ryan. "Ryan is really good with his little sister," says Mary. "Yes, they fight and can drive us crazy at times, but Ryan, and everyone on Ryan's soccer team, knows how to test Hannah's blood glucose level," adds Doug.

The good news is that the older Hannah gets, the more choices she can make for herself to help balance her diet, physical activities, and insulin injections so that she can maintain healthy control of her blood sugar levels. As Hannah becomes more independent, the easier it is becoming for her parents. Doug recounted an experience in which he encouraged Hannah in learning about the foods she needs to eat in order to obtain the proper amounts and balance of nutrients she requires at each meal, including carbohydrates. Says Doug, "At dinner the other day, Hannah said she was full. I told her that she needed to eat so she would get her carbs (carbohydrates). Hannah then asked, 'Dad, does my bread have carbs?' Yes, I told her. 'How about my meat?' No, I said. 'I guess I will eat my bread then,' she said." Hannah recognized the need to have her carbohydrates in order to stay healthy. The Beauregards try to make Hannah feel in control of her diabetes as much as possible by giving her choices. "We also always have a fallback food just in case Hannah doesn't want to eat what we have for dinner," Mary adds.

When Hannah reminded her bear Rufus that it was time for his evening shot, she was really announcing to her parents that she was ready to have her own shot. The lesson: If Rufus can do it, Hannah can do it, too.

As much as Doug and Mary sometimes feel they have things pretty much under control, "It's not easy being a parent of a child with diabetes, and it never will be," Doug says. The pre-school Hannah attends, for example, was leery at first about having a student with Hannah's disease, so the Beauregards had to educate the staff about diabetes and what to do if Hannah's blood glucose level is too low or too high. "Part of the problem," says Doug, "is that Hannah isn't always cooperative when her blood glucose level is low." The family has shied away from day care. When Hannah is not at pre-school, Doug's mother, Elizabeth—who is as well-trained as Doug and Mary in how to care for Hannah—spends two or three days a week at the Beauregard home. Doug adds that when he is at work "my students know that if my cell phone rings, it's something important."

In short, life is a constant vigil.

"Because Hannah is doing well, we want to get her story out to people. We feel we have something that we might be able to offer to other parents who are struggling with children who have this disease. It gives us strength."

Hannah is growing up to be an adorable little girl whose life will be in constant jeopardy until a cure is found for her type 1 diabetes. Until then, she will be required to take insulin every day of her life to survive.

"We're not angry that Hannah has (type 1) diabetes," says Doug. He and Mary just want to tell everyone they can about their little girl. "Because Hannah is doing well, we want to get her story out to people. We feel we have something that we might be able to offer to other parents who are struggling with children who have this disease. It gives us strength."

"We need to be strong for every child with diabetes," says Doug, "because without their parents, they won't make it."

PATIENT PROFILE

The NIDDK supports a multi-faceted research program that is investigating ways to help prevent, delay, or possibly cure type 1 diabetes and its complications. For example, the Epidemiology of Diabetes Interventions and Complications (EDIC), is a follow up to an earlier clinical trial in patients with type 1 diabetes. The results of this study continue to demonstrate the importance of beginning, as early as possible, intensive treatment to control blood sugar in order to prevent diabetes-related health complications.

Translating the positive results of research studies into improved care for patients with diabetes is an important aspect of the NIDDK mission. The recently published school guide, "Helping the Student with Diabetes Succeed: A Guide for School Personnel," is a key example of research-based efforts that can contribute to improved care for children with diabetes. This comprehensive guide for managing diabetes in the school setting was developed by the National Diabetes Education Program (NDEP), a collaborative initiative of the NIDDK and the Centers for Disease Control and Prevention. The NDEP uses over 200 public and private partnerships to promote application of research findings that have demonstrated value in the prevention of diabetic complications ensuing from both type 1 and type 2 diabetes, as well as in the prevention of type 2 diabetes. The guide sets out a team approach to diabetes management in schools and outlines the roles and responsibilities of all key school personnel, including school nurses, administrators, teachers, coaches and physical education instructors, bus drivers, lunchroom staff, and guidance counselors, as well as parents and students with diabetes. According to the guide, three key ingredients are needed to ensure successful teamwork:

- *All school staff members who have responsibility for students with diabetes have a basic understanding of the disease and the signs and symptoms of hypoglycemia and hyperglycemia.*
- *The school nurse and/or other trained personnel are available to assist with routine and emergency diabetes care tasks.*
- *Students with diabetes have the ability and are empowered to self-manage their disease as appropriate.*

Copies of the Guide are available for order or download from the NDEP website at http://www.ndep.nih.gov/resources/school.htm

*On the road to improving care for diabetes, the participation of patients in clinical studies is critical. A newly launched website provides patients with type 1 diabetes and their families with information on many of the clinical studies that are seeking volunteers (*http://www.niddk.nih.gov/fund/diabetesspecialfunds/*). This site also features information on research funding opportunities, research resources, and research consortia and networks for investigators studying type 1 diabetes and its complications.*

STOPPing Type 2 Diabetes

Once considered an "adult-onset" disease, type 2 diabetes is being increasingly diagnosed in children and adolescents—especially in minority populations. To address the rising tide of type 2 diabetes in young people, the NIDDK recently launched a new research program, Studies to Treat or Prevent Pediatric Type 2 Diabetes (STOPP-T2D). One facet of this program is a multicenter trial, Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY). TODAY is the first NIDDK-sponsored trial to focus on type 2 diabetes in youth. The TODAY trial will compare three treatments for type 2 diabetes in children and teens in 12 medical centers and their affiliated sites across the United States, in order to identify the best therapeutic strategies to combat this disease in young people.

A Rising Tide: Type 2 Diabetes in Youth

About 18.2 million people—6.3 percent of the U.S. population—have diabetes. It is the main cause of kidney failure, lower limb amputations, and new-onset blindness in adults, and is a major cause of heart disease and stroke. Type 2 diabetes, most common in adults over age 40, accounts for up to 95 percent of all diabetes cases. People with type 2 diabetes are impaired in their ability to produce and respond to insulin, a hormone whose proper action is required for the body to absorb and use the sugar glucose as a cellular fuel. The prevalence of type 2 diabetes has risen dramatically in the last 30 years. In the last 10 years alone, the prevalence of diagnosed diabetes cases increased 50 percent, due mostly to the upsurge in obesity in the United States.

However, type 2 diabetes is no longer restricted to adults. Type 2 diabetes has been rising steadily in all children, but especially among African American, Hispanic American and American Indian adolescents, according to reports from clinics around the country. Studies in a number of cities report that childhood type 2 diabetes cases have risen dramatically. By the 1990s, type 2 diabetes accounted for 8 to 45 percent of new childhood diabetes cases, depending on geographic location.

In both adults and children, type 2 diabetes is closely linked to being overweight, inactive, and having a family history of diabetes. According to the 1999 to 2002 National Health and Nutrition Examination Survey (NHANES), about 16 percent of young people ages 6 to 19 are overweight—nearly triple the 1980 rate. Genetic susceptibility, lack of physical activity and unhealthy eating patterns all play important roles in determining a child's weight, the risk for type 2 diabetes, and other complications of being overweight.

Implications of Early Onset

The longer a person has diabetes, the greater the chances he or she will sustain serious damage to the eyes, nerves, heart, kidneys, and blood vessels. This aspect of diabetes makes the growing burden of type 2 diabetes in children particularly alarming, as children with this diagnosis have a greater statistical chance of developing medical complications during their lifetimes. Primary prevention of type 2 diabetes in youth is therefore a key public health goal. However, optimizing type 2 diabetes treatment options is equally critical, in order to forestall the onset of complications in children who already have the disease.

The TODAY Trial

Therapeutic strategies for type 2 diabetes need to address the primary metabolic abnormality of this disease, which also underlies many of its complications—the inability to maintain blood sugar levels within a normal range. Many drugs are available to treat type 2 diabetes in adults, but metformin, which lowers the liver's production of glucose, is the only oral drug approved by the Food and Drug Administration to treat type 2 diabetes in children. The TODAY trial is examining the use of both metformin and another oral drug currently approved for adults only, rosiglitazone. Rosiglitazone belongs to a class of insulin-sensitizing drugs called the thiazolidinediones (TZDs). It helps muscle cells respond to insulin and use glucose more efficiently.

Enrollment in the TODAY trial began in Spring 2004 and is expected to continue for 3 years. TODAY participants will be randomly assigned to one of three treatment groups: metformin alone; metformin and rosiglitazone in combination; and metformin plus intensive lifestyle

change aimed at improving nutrition and increasing physical activity, with a goal of losing weight. Researchers plan to enroll 750 children and teens 10 to 17 years old diagnosed with type 2 diabetes in the past 2 years. The trial is expected to last 5 years.

The TODAY study's main goal is to determine how well and for how long each treatment approach controls blood glucose levels. The study will also evaluate:

- Safety of the treatments;
- Effects of the treatments on the following: insulin production; insulin resistance (a term denoting when cells do not effectively use insulin); body composition; nutrition; physical activity and aerobic fitness; risk factors for eye, kidney, nerve, and heart disease; quality of life; and psychological outcomes;
- Influence of individual and family behaviors on treatment response; and
- Cost-effectiveness of the treatments.

TODAY is the first clinical study to look at the effects of intensive lifestyle change aimed at lowering weight by cutting calories and increasing physical activity in youths with type 2 diabetes. The NIDDK-sponsored Look AHEAD trial is currently studying the benefits of weight loss in adults with type 2 diabetes. The TODAY trial is one of two NIDDK-funded studies that will focus on type 2 diabetes in children. An anticipated prevention study, currently in its pilot phase, will seek to develop cost-effective interventions that can be widely applied in schools across the country.

In a March 15, 2004 press release announcing the start of the TODAY study, then-HHS Secretary Tommy G. Thompson noted that: "Obesity and type 2 diabetes are among the most serious health challenges facing America's youth today. We need to do all we can to develop strategies that encourage healthy eating and active lifestyles in our children." By supporting major research studies aimed at the twin goals of optimal treatment and prevention of type 2 diabetes in children, the NIDDK hopes to ameliorate and possibly reverse the onset of this disease and its complications in this most vulnerable population.

TODAY Snapshot:
Participant Bethannie Ramirez


Bethannie Ramirez

Bethannie Ramirez is bright, mature, and articulate—and at the age of 13 was diagnosed with type 2 diabetes. Now 15 and a freshman in high school, Bethannie says that her diagnosis came as a real shock. "I thought, 'this couldn't happen to me!' But then I gradually started to accept it and said to myself, I might as well deal with it the best I can." Bethannie, who sports a 3.9 grade-point-average and is an avid reader—especially of the "Harry Potter" series—aspires to be a screen writer or perhaps even an actress one day. During one of her follow-up medical examinations, she was asked if she would be interested in taking part in the TODAY clinical trial. "I decided I would, not only for myself, but to help other kids my age better understand this disease and what they can do to help themselves," she says. With her parents' consent, she enrolled in the TODAY study in November 2004.

Bethannie, who is of Philippine decent and whose grandmother and uncle—both on her mother's side—have been diagnosed with type 2 diabetes, says that being part of the study is fitting into her life. "I take my medication, watch what I eat, and otherwise live normally," she says. She is also quick to add that she's happy with losing weight as a result of her participation in the study and that her high school friends are very supportive. "When I first was diagnosed, I didn't want to tell anyone," says Bethannie. "I told one person; then others found out. But no one pities me. They understand what I need to do [for my health] and respect me for doing it."

Bethannie's mother, Elizabeth, says she's very happy she enrolled Bethannie in the study and very proud that her daughter is volunteering to help other teenagers with type 2 diabetes. "She loves to volunteer for things," Elizabeth says. As for Bethannie, who likes to write poems and stories, she says that it is highly likely that one day she will write about her diabetes—and maybe even about taking part in the TODAY study.

National Diabetes Education Program (NDEP)

Through education and awareness campaigns and other health information dissemination efforts, the NDEP aims to improve treatment and outcomes for people with diabetes, to promote early diagnosis, and to help prevent the onset of diabetes. The program develops information and education messages and materials for people with diabetes and their families, health care providers, payers and purchasers of health care, health care system policymakers, and the general public—including people with undiagnosed diabetes and those at risk for the disease. The NDEP is jointly sponsored by the NIDDK and the Division of Diabetes Translation of the Centers for Disease Control and Prevention, both of the U.S. Department of Health and Human Services, and also involves the participation of over 200 public and private partner organizations.

The NDEP's "Small Steps. Big Rewards. Prevent Type 2 Diabetes" campaign is based on the findings of the NIH-sponsored Diabetes Prevention Program (DPP) clinical trial. The DPP demonstrated that the risk of developing type 2 diabetes can be significantly reduced through modest weight loss, of 5 to 7 percent of body weight, and exercise, such as 30 minutes of moderate physical activity five days per week. To reach those groups at high risk for type 2 diabetes, in 2004 the NDEP launched the first national multicultural diabetes prevention campaign, with tailored materials and messages for high-risk audiences. Campaign materials include motivational tip sheets, as well as print and radio public-service ads. For African-Americans, the NDEP's campaign is called, "More Than 50 Ways To Prevent Diabetes," and uses humor to encourage healthy lifestyle changes. For a Hispanic audience, the NDEP launched the campaign, "Prevengamos la Diabetes Tipo 2: Paso a Paso" (Let's Prevent Type 2 Diabetes: Step by Step). Campaign materials include a music CD, performed by Hispanic recording artists, to promote physical activity. For American Indians and Alaska Natives, the NDEP launched the public awareness campaign, "We Have the Power To Prevent Diabetes." The campaign uses testimonials from American Indians and Alaska Natives who have made lifestyle changes to prevent diabetes. For Asian Americans and Pacific Islanders, the NDEP's campaign, "Two Reasons I Find Time To Prevent Diabetes...My Future and Theirs," uses an inter-generational appeal to encourage people to make healthy lifestyle changes. The NDEP also is reaching out to older adults with the campaign, "It's Not Too Late To Prevent Diabetes. Take Your First Step Today." To help promote the campaign, NDEP has assembled a team of people from across the country who are working to prevent diabetes in their own lives and in their communities. Finally, for a general audience, the campaign has the message, "Get Real! You Don't Have To Knock Yourself Out To Prevent Diabetes." In 2005 the NDEP is adding a new target audience to promote diabetes prevention messages—women with a history of gestational diabetes and their children. Further information can be found at *http://ndep.nih.gov/campaigns/SmallSteps/SmallSteps_index.htm*.

In other activities, the NDEP continues to partner with the American Diabetes Association for the health awareness campaign, "Be Smart About Your Heart: Control the ABCs of Diabetes" to promote the link between diabetes and cardiovascular disease. Versions of the campaign are also tailored for Hispanic and Latino Americans and for Asian Americans and Pacific Islanders. The NDEP also offers other patient education materials and resources and tools designed for health care professionals, such as a new interdisciplinary primer for pharmacists, podiatrists, optometrists and dental professionals to promote a team care approach to comprehensive diabetes care with a companion supplement for controlling blood glucose, pressure and cholesterol. The NDEP web site (*betterdiabetescare.nih.gov*) provides information on making changes in systems of care that can lead to better delivery of care for people with diabetes. In 2004 NDEP revised the

publication, “Guiding Principles of Diabetes Care” outlining the seven essential components of quality diabetes care. The NDEP continues to provide the publication, “Helping the Student with Diabetes Succeed: A Guide for School Personnel,” and has developed a series of tip sheets for children with type 2 diabetes. For the worksite, the NDEP has a Web-based resource for employers and others; Spanish lesson plans were launched on the Website this past year to meet the growing need for Hispanic/Latino materials in the business community. The NDEP is beginning an initiative to determine the economic impetus for diabetes prevention and control. Further information on NDEP activities and materials can be found on the NDEP Website at: *http://ndep.nih.gov/index.htm*.

Enzyme Replacement Therapy for Lysosomal Storage Disorders

The body's cells recycle many of the substances they no longer need by digesting them with enzymes inside cellular compartments called lysosomes. If these enzymes are missing or defective due to genetic mutations, toxic waste products are not properly degraded. Instead, they build up in the lysosomes and lead to severe organ damage. Diseases caused by these enzyme deficiencies, referred to as lysosomal storage disorders, are individually rare, but collectively affect about 1 in 7,700 infants born in the United States.[1] Symptoms vary, and are often not apparent at birth; however, as the undigested materials accumulate, they can cause serious problems such as weakness, severe pain, brittle bones, mental retardation, corneal clouding, organ failure and death.

Lysosomal storage disorder research, built on substantial NIH investments followed by recent commercial product development, is a classic story of translating remarkable findings from basic research into Food and Drug Administration-approved treatments for three of these serious disorders: mucopolysaccharidosis I (MPS I), Gaucher disease and Fabry disease. The critical discovery dates to work in the late 1960s, when NIDDK intramural researchers found that growth medium taken from a culture of normal cells relieved the lysosomal storage defect of cells cultured from a patient with MPS I. In essence, this meant that normal cells secrete the enzyme missing in MPS I patients; and more importantly, the MPS I cells can internalize that enzyme from the medium, and somehow send it to the lysosome, right where it needs to go. It was later discovered that this secretion and re-uptake process is a pathway common to many of the enzymes absent in these disorders. Thus, in theory, patients with such a disease might be treatable by administering purified forms of the enzymes they need—an approach referred to as enzyme replacement therapy.

Indeed, experiments in the 1970s suggested that an enzyme-replacement approach could be beneficial. For example, in separate but related work, NIH intramural scientists and NIDDK grantees treated Gaucher and Fabry patients with the enzymes they lacked, which the researchers had purified from human tissue. These studies were of short duration, and the long-term health effects could not be determined. However, the accumulation of undigested lysosomal materials was significantly reduced for a period of time after treatment, at least in some parts of the body. Therefore, researchers theorized that, if adequate supplies of the enzymes could be produced, there was reasonable hope that they might be effective therapeutically.

Tremendous advances in gene manipulation technology in the 1980s made it possible to isolate the normal versions of genes mutated in patients with lysosomal storage disorders. Researchers showed that active, properly modified, human lysosomal enzymes could be produced in cultured mammalian cells. With this technology, comparatively large amounts of the enzymes could be produced and purified—far more inexpensively and easily than was previously possible.

However, there was a pressing need for an animal model of a lysosomal storage disorder to facilitate studies of the long-term safety and efficacy of such treatments. Therefore, another key finding was that a natural mutation occurring in some breeds of dogs eliminates the same enzyme that is missing in MPS I

patients. Because these dogs have symptoms quite similar to those of humans with the disease, they are a useful animal model that enabled pilot-tests of therapeutic strategies.

The combination of an improved enzyme supply and an animal model permitted testing of intravenous enzyme replacement therapy in MPS I dogs over a three month period. Some dogs developed immune reactions against the enzyme, but the problem could be managed through pre-medication with antihistamines and slower administration of the enzyme. More importantly, although lysosomal function remained unimproved in some parts of the body, including the brain, it was normalized in certain organs and greatly improved in others. With further work, methods were developed that avoided immune reactions from the animals, and enabled long-term treatment studies, as a prelude to clinical trials.

These ground-breaking basic and pre-clinical research advances were ultimately translated into valuable therapeutics by drug companies. Largely as a result of this translational research, the Food and Drug Administration granted approval for treatment of Gaucher, Fabry and MPS I patients with genetically engineered forms of their respective missing enzymes. The National Organization for Rare Diseases recognized this achievement by presenting its 2004 Corporate Awards to two of the companies which brought these products to market by building upon the earlier NIH-funded discoveries. Treatments for several more lysosomal storage disorders are currently in phase III clinical trials, and are likely to come to market soon.

As remarkable as these advances are, and although the improvements in quality of life for lysosomal storage disorder patients are potentially very significant, these treatments are not cures. Patients may have to see their physicians weekly to receive lengthy infusions of the enzymes. Moreover, some disease manifestations are unlikely to be alleviated, such as the corneal clouding, bone disease and mental retardation that often occur in MPS I patients. Therefore, the NIDDK continues to encourage research on lysosomal storage disorders.

One promising area for developing treatments that might avoid some of these limitations is the discovery of small molecules that can stabilize defective enzymes in patients in whom they are not entirely absent. To explore opportunities in this field, the NIDDK sponsored a workshop on “Protein Misfolding and Misprocessing in Disease.” As part of its Roadmap Initiative, the NIH is establishing small molecule screening facilities, which could speed up the process of identifying new therapeutics for lysosomal storage disorders.

[1] Meikle PJ, Hopwood JJ, Clague AE, and Carey WF. Prevalence of lysosomal storage disorders. *JAMA* 281: 249-254, 1999.

Denise Dengel

Living with MPS I Has Turned Her World Upside Down

Denise Dengel was once an avid outdoorswoman who loved to compete in equestrian barrel racing, hike and camp, work out at the gym, and ride mountain bikes with her friends. She says she remembers what it was like to be healthy, to feel good, to be working and living life to the fullest. "I was a very active woman," says 40-year-old Denise, who was forced to give up what she refers to as her "turbocharged" life by the time she reached her early 30s because of a rare metabolic disease, called MPS I.

MPS is shorthand for a group of seven inherited metabolic diseases called mucopolysaccharidoses. Over time, these diseases wreak havoc on joints and organs, resulting in permanent damage that can affect an individual's appearance, physical abilities, organ and system functions, and, in most cases, mental development. Denise's disease, MPS I, can be mild, intermediate, or severe, with symptoms ranging from joint stiffness and slow progression of physical problems in its milder form, to serious cognitive and physical impairment early on, and death in childhood at its most severe.

Unlike many MPS I patients, Denise has a relatively mild form of the disease, called MPS I, Scheie syndrome (MPS I S). Nevertheless, in recent years, this painful, incurable and insidious disease has dramatically affected her life, and without the development of fully effective treatments, will more than likely continue to do so.

Since the mid-1990s, Denise has had several operations, including two open heart surgeries,

Denise Dengel

an operation on each hand to correct for carpal tunnel syndrome, and another to remove toxic deposits on her spinal cord. She experiences headaches that she says feel "like a knife in my head." Her joints have stiffened to such a degree that she has had to give up most, if not all, of her physical activities, and her cognitive skills have decreased to the point that she has left her full-time job as a social worker and is now on long-term disability. Says Denise of her earlier, more healthy and active years: "I know what that world is like, and if I can't have it back, at the very least I don't want the world I currently live in to get any worse."

Hope Through Research

Research supported by the NIDDK has led to the development of the drug, Aldurazyme®, recently approved by the FDA as a treatment option for MPS I patients. (See also "Story of Discovery: Enzyme Replacement Therapy for Lysosomal Storage Disorders.")

PATIENT PROFILE

Denise began taking Aldurazyme® about a year and a half ago. She believes the drug has made her joints less stiff and thereby has greatly increased her flexibility. However, it is unlikely that Aldurazyme® will improve the cognitive and other brain-related symptoms Denise is experiencing because Aldurazyme® does not cross the blood-brain barrier—a special barrier system that protects the brain from absorbing harmful substances from blood. Thus, the NIDDK also is focusing its efforts on supporting research on methods, such as gene therapy, which may be able to prevent or treat brain damage in this disease. In the meantime, Denise says that, since taking Aldurazyme®, her joints "haven't gotten any worse," and adds that she is excited to see if this drug can at the very least stabilize her condition or better yet, improve it over time. "I get large doses of the enzyme I'm lacking. The hope is that the body takes up enough of it to retard or reverse the degenerative process that's taking place," she says.

About MPS

MPS is caused by the absence or malfunctioning of certain enzymes needed to break down glycosaminoglycans—long chains of sugar molecules used by cells to help build bone, cartilage, tendons, corneas, skin and connective tissue. (Glycosaminoglycans used to be called "mucopolysaccharides," hence the name of the disease.) Glycosaminoglycans, or GAGs, are also found in the fluid that lubricates joints. When these long sugar chains need to be broken down and recycled, cells haul them into special enzyme-filled compartments, called lysosomes, for digestion. People with MPS either do not produce enough of one of the 11 enzymes required to break down the GAGs into simple molecules, or they produce enzymes that do not work properly. In either case, the result is a toxic build-up of waste molecules in the body, as the lysosomes become engorged. Denise describes people with the disease as "being clogged everywhere with (GAGs), in our joints, as well as our organs."

There are many forms of MPS. MPS I S, Scheie syndrome, is the mildest form of MPS I. Symptoms, which include stiff joints, generally begin to appear after age five; a diagnosis is made most commonly after age 10. Children with MPS I S have normal intelligence or may have mild learning disabilities; some may have psychiatric problems. Glaucoma, retinal degeneration, and clouded corneas may significantly impair vision and eventually lead to blindness in adulthood. Other problems include carpal tunnel syndrome or other nerve compression, stiff joints, claw hands and deformed feet, a short neck, and aortic valve disease. Some affected individuals also have obstructive airway disease and sleep apnea. Unlike patients with many other forms of MPS, those with MPS I S can live into adulthood.

All forms of MPS, except MPS II, or Hunter Syndrome, are autosomal recessive disorders. This term means that only individuals inheriting the defective gene from both parents are affected. In Hunter Syndrome, the mother alone may pass the defective gene to a son.

Living with MPS I, Scheie Syndrome

Developmentally, Denise had a normal childhood, which even included horseback riding. But at some point her mother noticed that both Denise and her brother just didn't move like other children. "My brother's and my joints were beginning to stiffen from (GAG) build-up to the point where I couldn't get on my horse without assistance," says Denise. She and her older brother by 18 months were diagnosed with MPS I in 1975, when Denise was 10. Despite its genetic origins, there is no other known history of MPS in the Dengel family.

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At the time the siblings were diagnosed, not much was known about MPS. Both Dengel children were relatively mildly affected, and because neither was cognitively challenged by the disease, they were studied by researchers trying to find out more about this rare disease. Sadly, Denise's brother, with whom she was very close, died in an automobile accident at age 18.

"Up until I was 25, I firmly believed that I had a disease that would only affect my joints. I thought that as I got older they would just continue to stiffen, and that nothing else was the matter with me," says Denise. Unfortunately, she was wrong. By her mid-20s, Denise began having problems with her hands, which led to carpal tunnel syndrome. Moreover, unbeknownst to her at the time, the disease was insidiously affecting other parts of her body as well, including her spine, heart, lungs and brain. "It has progressed to the point that today I'm a seriously affected adult with MPS I," says Denise.

By 1996, Denise was getting weaker and the disease was beginning to show up in her organs. For example, an MRI showed a build-up of GAG pressing on her spinal cord, so in 1997 she had spinal surgery near her brain stem. Unfortunately, because of its location, physicians could not remove all of the toxic material. In 1999, Denise had the aortic valve in her heart replaced with a tissue valve. Because of continued GAG build-up, the valve needed to be replaced again by 2002, this time with a synthetic component.

Denise says she suffers from neurological issues that include extreme headaches and dizziness. An MRI indicates that she also has lesions on the brain and is manifesting symptoms for hydrocephalus (water on the brain). "Sometimes I can't think clearly and my words become slurred. I often feel nauseated and suffer from chronic fatigue. If I'm lucky, I can function fairly well for two to four hours a day," she says. In 1998, because of these worsening conditions, Denise, who for 10 years gained great satisfaction from working with homeless youth in Seattle, Washington, quit her job as a social worker. But she's never given up on her life.

"I only know five people older than I am with my form of MPS who are still alive, and some of them are blind. I want nothing more than for research to change all of this within my lifetime."

"My family and friends are a great support system," says Denise. "I probably wouldn't be able to live as independently as I do without them." In 1996, Denise joined the MPS Society and served as a board member for two years. She says the society has become a "real mainstay" in her life. "We're a bunch of people trying to live the best that we can with what we've got," says Denise. She adds, "I only know five people older than I am with my form of MPS who are still alive, and some of them are blind. I want nothing more than for research to change all of this within my lifetime." She is currently a member of the MPS Society's federal legislative committee, which supports research efforts to help people with MPS. She's very excited about how much has been learned about MPS in recent years. "I'm a true believer in advocacy and education," says Denise.